

of said clarified harvest with an increase in a titer of said host cells cultured in said CDM compared to aflibercept produced by said host cells cultured in said CDM where said metal concentration is not decreased.

23. A method of increasing production of aflibercept harvested from a host cell cultured in a chemically defined medium (CDM) and reducing aflibercept sample color, comprising:

- (a) providing said host cell genetically engineered to express aflibercept;
- (b) culturing said host cell in said CDM under suitable conditions in which said host cell expresses aflibercept;
- (c) harvesting aflibercept produced by said host cell forming a harvest comprising aflibercept wherein:
 - i. the cumulative concentration of iron in said CDM is less than or equal to about 55.0 μ M;
 - ii. the cumulative concentration of copper in said CDM is less than or equal to about 0.8 μ M;
 - iii. the cumulative concentration of nickel in said CDM is less than or equal to about 0.4 μ M;
 - iv. the cumulative concentration of zinc in said CDM is less than or equal to about 56 μ M;
 - v. the cumulative concentration of cysteine in said CDM is less than 10 mM; and/or
 - vi. including one or more anti-oxidant in said CDM wherein the concentration of said anti-oxidant is about 0.001 mM to about 10.0 mM for any single anti-oxidant.

24. The method of claim **23**, wherein a titer of said host cells cultured in CDM to produce aflibercept is increased in

comparison to a titer of host cells cultured in CDM exceeding one or more of said cumulative concentrations of (i)-(vi) while said sample color is no more yellow brown than European Color Standard BY2 when the concentration of protein in said harvest is normalized to 5.0 g/L.

25. The method of claim **23**, wherein said cumulative concentration of anti-oxidants in said CDM is about 0.001 mM to about 10.0 mM for any single anti-oxidant and the cumulative concentration of all anti-oxidants is no more than about 30.0 mM.

26. The method of claim **24**, wherein said sample color is no more yellow brown than European Color Standard BY3 when the concentration of protein in said harvest is normalized to 5.0 g/L.

27. The method of claim **23**, wherein said reduced sample color has a b* value that is reduced by about 45% compared to an aflibercept sample color obtained by harvesting aflibercept produced by said host cell forming a harvest comprising aflibercept wherein one or more concentration of (i) to (vi) are not maintained.

28. The method of claim **23**, wherein said anti-oxidant is taurine, hypotaurine, glycine, thiocetic acid, glutathione, choline, hydrocortisone, Vitamin C, Vitamin E or combinations thereof.

29. The method of claim **23**, wherein said CDM includes uridine, manganese, galactose or combinations thereof.

30. The method of claim **23**, wherein there is no significant increase or decrease in titer, viable cell concentration, viability, ammonia or osmolality.

* * * * *